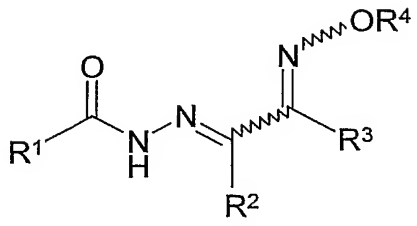
Claims

1. A use of a compound of formula I,



I

wherein

the squiggly bonds represent optional *E* or *Z* geometry;

R^1 and R^2 independently represent an aryl group or a heteroaryl group, both of which groups are optionally substituted by one or more substituents selected from:

X^1, C_{1-8} alkyl, an aryl group and a heterocyclic group:-

(A) which C_{1-8} alkyl group is itself optionally substituted by one or more Z substituents; and

(B) which C_{1-8} alkyl, aryl and heterocyclic groups may themselves be substituted by one or more substituents selected from X^1, C_{1-8} alkyl (which latter group may be further substituted by one or more substituents selected from X^1, C_{1-8} alkyl, an aryl group, a heterocyclic group and Z), an aryl group and a heterocyclic group (and which latter two groups may be further substituted by one or more substituents selected from X^1, C_{1-8} alkyl, an aryl group and a heterocyclic group), in which:-

X^1 represents, on each occasion when used above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^1-R^5$, wherein:

A^1 represents a spacer group selected from $-C(Z)A^2-$, $-N(R^6)A^3-$, $-OA^4-$, $-S-$ or $-S(O)_nA^5-$, in which:

A^2 represents a single bond, $-O-$, $-S-$, $-N(R^6)A^6-$ or $-C(Z)-$;

A^3 represents A^6, $-C(Z)N(R^6)C(Z)N(R^6)-$, $-C(Z)N(R^6)C(Z)O-$, $-C(Z)N(R^6)S(O)_nN(R^6)-$, $-C(Z)S-$, $-S(O)_n-$, $-S(O)_nN(R^6)C(Z)N(R^6)-$, $-S(O)_nN(R^6)C(Z)O-$ or $-S(O)_nN(R^6)S(O)_nN(R^6)-$;

A^4 represents A^6 or $-S(O)_n-$;

A^5 represents a single bond, $-N(R^6)-$ or $-O-$;

A^6 represents, on each occasion when used above, a single bond, $-C(Z)-$, $-C(Z)O-$, $-C(Z)N(R^6)-$, $-S(O)_nN(R^6)-$ or $-S(O)_nO-$; and

Z represents, on each occasion when used above, a substituent connected by a double bond, which is selected from $=O$, $=S$, $=NR^5$, $=NN(R^5)(R^6)$, $=NOR^5$, $=NS(O)_2N(R^5)(R^6)$, $=NCN$, $=C(H)NO_2$ and $=C(R^5)(R^6)$;

R^5 and R^6 independently represent, on each occasion when used above,

(a) hydrogen;

(b) C_{1-8} alkyl, optionally substituted by one or more substituents selected from X^2, Q, C_{1-8} alkyl (optionally substituted by one or more substituents selected from X^2, C_{1-8} alkyl, an aryl group, a heterocyclic group and Q), an aryl group and a heterocyclic group (which latter two groups are optionally substituted by one or more substituents selected from X^2, C_{1-8} alkyl, an aryl group and a heterocyclic group); or

(c) an aryl group or a heterocyclic group, both of which are optionally substituted by one or more substituents selected from X^2, C_{1-8} alkyl (optionally substituted by one or more substituents selected from X^2, C_{1-8} alkyl, an aryl group, a heterocyclic group and Q), an aryl group and a heterocyclic group (which latter two groups are optionally

substituted by one or more substituents selected from X^2, C_{1-8} alkyl, an aryl group and a heterocyclic group); or

R^5 and R^6 may, when present on the same atom or on adjacent atoms, taken together with those atoms form a 5- to 8-membered ring optionally containing 1 to 3 heteroatoms and/or 1 to 3 double bonds, which ring is itself optionally substituted by one or more substituents selected from X^2, C_{1-8} alkyl, an aryl group, a heterocyclic group (which latter three groups are optionally substituted as described in (b) and (c) above, respectively) and, provided that the ring that R^5 and R^6 may together be part of is not aromatic in character, Q;

X^2 represents, on each occasion when used above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^7-R^7$, wherein:

A^7 represents a spacer group selected from $-C(Q)A^8-$, $-N(R^8)A^9-$, $-OA^{10}-$, -S- or $-S(O)_nA^{11}-$, in which:

A^8 represents a single bond, -O-, -S-, $-N(R^8)-$ or -C(Q)-;

A^9 represents A^{12}, $-C(Q)N(R^8)C(Q)N(R^8)-$, $-C(Q)N(R^8)C(Q)O-$, $-C(Q)N(R^8)S(O)_nN(R^8)-$, -C(Q)S-, $-S(O)_n-$, $-S(O)_nN(R^8)C(Q)N(R^8)-$, $-S(O)_nN(R^8)C(Q)O-$ or $-S(O)_nN(R^8)S(O)_nN(R^8)-$;

A^{10} represents A^{12} or $-S(O)_n-$;

A^{11} represents a single bond, $-N(R^8)-$ or -O-;

A^{12} represents, on each occasion when used above, a single bond, -C(Q)-, $-C(Q)O-$, $-C(Q)N(R^8)-$, $-S(O)_nN(R^8)-$ or $-S(O)_nO-$;

Q represents, on each occasion when used above, a substituent connected by a double bond, which is selected from =O, =S, $=NR^7$, $=NN(R^7)(R^8)$, $=NOR^7$, $=NS(O)_2N(R^7)(R^8)$, =NCN, $=C(H)NO_2$ and $=C(R^7)(R^8)$;

R^7 and R^8 independently represent, on each occasion when used herein,

(i) hydrogen;

(ii) an aryl group or a heterocyclic group, both of which may be substituted by one or more substituents selected from X^3, C_{1-8} alkyl, an aryl group and a heterocyclic group (and which latter three groups are themselves optionally substituted by one or more substituents selected from halo, hydroxy, $-R^9$, $-OR^9$ and, provided that the group is not aromatic in nature, =O); or

(iii) C_{1-8} alkyl, optionally substituted by one or more substituents selected from X^3 and W; or

R^7 and R^8 may, when present on the same atom or on adjacent atoms, taken together with those atoms form a 5- to 8-membered ring optionally containing 1 to 3 heteroatoms and/or 1 to 3 double bonds, which ring is itself optionally substituted by one or more substituents selected from X^3, C_{1-8} alkyl, an aryl group, a heterocyclic group and, provided that the ring that R^7 and R^8 may together be part of is not aromatic in character, W;

X^3 represents, on each occasion when used above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^{13}-R^{10}$, wherein:

A^{13} represents a spacer group selected from $-C(W)A^{14}-$, $-N(R^{11})A^{15}-$, $-OA^{16}-$, -S- or $-S(O)_nA^{17}-$, in which:

A^{14} represents a single bond, -O-, -S-, $-N(R^{11})-$ or -C(W)-;

A^{15} represents A^{18}, $-C(W)N(R^{11})C(W)N(R^{11})-$, $-C(W)N(R^{11})C(W)O-$, $-C(W)N(R^{11})S(O)_nN(R^{11})-$, -C(W)S-, $-S(O)_n-$, $-S(O)_nN(R^{11})C(W)N(R^{11})-$, $-S(O)_nN(R^{11})C(W)O-$ or $-S(O)_nN(R^{11})S(O)_nN(R^{11})-$;

A^{16} represents A^{18} or $-S(O)_n-$;

A^{17} represents a single bond, $-N(R^{11})-$ or -O-;

A^{18} represents, on each occasion when used above, a single bond, -C(W)-, -C(W)O-, $-C(W)N(R^{11})-$, $-S(O)_nN(R^{11})-$ or $-S(O)_nO-$;

R^9 represents, on each occasion when used above, C_{1-6} alkyl optionally substituted by one or more fluoro atoms;

W represents, on each occasion when used above, a substituent connected by a double bond, which is selected from =O, =S, $=NR^{10}$, $=NN(R^{10})(R^{11})$, $=NOR^{10}$, $=NS(O)_2N(R^{10})(R^{11})$, =NCN, $=C(H)NO_2$ and $=C(R^{10})(R^{11})$;

R^{10} and R^{11} independently represent, on each occasion when used above:

(1) hydrogen;

(2) an aryl group or a heterocyclic group, both of which may be substituted by one or more substituents selected from X^4, C_{1-8} alkyl, methylenedioxy, difluoromethylenedioxy and dimethylmethylenedioxy; or

(3) C_{1-8} alkyl, optionally substituted by one or more substituents selected from X^4, =O, =S, $=NR^{12}$, $=NN(R^{12})(R^{13})$, $=NOR^{12}$, $=NS(O)_2N(R^{12})(R^{13})$, =NCN, $=C(H)NO_2$ and $=C(R^{12})(R^{13})$; or

R^{10} and R^{11} may, when present on the same atom or on adjacent atoms, taken together with those atoms form a 5- to 8-membered ring optionally containing 1 to 3 heteroatoms and/or 1 to 3 double bonds, which ring is itself optionally substituted by one or more substituents selected from X^4 and, provided that the ring that R^{10} and R^{11} may together be part of is not aromatic in character, =O, =S, $=NR^{12}$, $=NN(R^{12})(R^{13})$, $=NOR^{12}$, $=NS(O)_2N(R^{12})(R^{13})$, =NCN, $=C(H)NO_2$ and $=C(R^{12})(R^{13})$;

X^4 represents, on each occasion when used above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^{19}-R^{12}$, wherein:

A^{19} represents a spacer group selected from $-C(O)A^{20}-$, $-N(R^{13})A^{21}-$, $-OA^{22}-$, -S- or $-S(O)_nA^{23}-$, in which:

A^{20} represents a single bond, -O-, -S-, $-N(R^{13})-$ or -C(O)-;

A^{21} represents A^{24}, $-C(O)N(R^{13})C(O)N(R^{13})-$, $-C(O)N(R^{13})C(O)O-$, $-C(O)N(R^{13})S(O)_nN(R^{13})-$, -C(O)S-, $-S(O)_n-$, $-S(O)_nN(R^{13})C(O)N(R^{13})-$, $-S(O)_nN(R^{13})C(O)O-$ or $-S(O)_nN(R^{13})S(O)_nN(R^{13})-$;

A^{22} represents A^{24} or $-S(O)_n-$;

A^{23} represents a single bond, $-N(R^{13})-$ or $-O-$;

A^{24} represents, on each occasion when used above, a single bond, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_nN(R^{13})-$ or $-S(O)_nO-$;

R^{12} and R^{13} independently represent, on each occasion when used above:

(A) hydrogen; or

(B) C_{1-6} alkyl, optionally substituted by one or more substituents selected from halo, $-N(R^{14})R^{15}$, $-OR^{15}$ and =O;

n represents, on each occasion when used above, 1 or 2;

R^3 and R^4 independently represent H or C_{1-6} alkyl optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl, cyano, $-NO_2$, $-ONO_2$, $-N(R^{14})R^{15}$, $-OR^{15}$, =O, aryl and heteroaryl; and

R^{14} and R^{15} independently represent, on each occasion when used above, H or C_{1-4} alkyl,

or a pharmaceutically acceptable salt thereof,

for the manufacture of a medicament for the treatment of a disease in which inhibition of the activity of a lipoxygenase, and particularly 15-lipoxygenase, is desired and/or required.

2. A use as claimed in Claim 1, wherein R^1 represents a phenyl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from X^1, aryl and C_{1-6} alkyl, which alkyl group is optionally substituted by one or more groups selected from X^1.

3. A use as claimed in Claim 1 or Claim 2, wherein R^2 represents a phenyl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from X^1, a heterocyclic group and C_{1-3} alkyl, which alkyl group is optionally substituted by X^1.

4. A use as claimed in any one of the preceding claims, wherein X^1 represents halo, $-NO_2$, $-A^1-R^5$ or cyano.

5. A use as claimed in any one of the preceding claims, wherein A^1 represents $-N(R^6)A^3-$, $-OA^4-$ or $-S(O)_nA^5-$.

6. A use as claimed in any one of the preceding claims, wherein A^2 represents a single bond, -O- or $-N(R^6)A^6-$.

7. A use as claimed in any one of the preceding claims, wherein A^3 represents A^6 or $-S(O)_n-$.

8. A use as claimed in any one of the preceding claims, wherein A^4 represents A^6.

9. A use as claimed in any one of the preceding claims, wherein A^5 represents $-N(R^6)-$.

10. A use as claimed in any one of the preceding claims, wherein A^6 represents a single bond.

11. A use as claimed in any one of the preceding claims, wherein n represents 2.

12. A use as claimed in any one of the preceding claims, wherein R^5 represents H, C_{1-3} alkyl or phenyl.

13. A use as claimed in any one of the preceding claims, wherein R^6 represents H or C_{1-3} alkyl.

14. A use as claimed in any one of the preceding claims, wherein R^3 represents H or C_{1-3} alkyl.

15. A use as claimed in any one of the preceding claims, wherein R^4 represents H or C_{1-3} alkyl, which alkyl group is optionally substituted by one or more substituents selected from phenyl and $-OR^{15}$.

16. A use as claimed in any one of the preceding claims, wherein R^{15} represents C_{1-2} alkyl.

17. A use as claimed in any one of the preceding claims, wherein R^1 and/or R^2 represent an optionally substituted pyrrolidinyl, piperidinyl, oxindolyl, phenyl, naphthyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, indolyl, indolinyl, isoindolinyl, quinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinolizinyl, benzofuranyl, isobenzofuranyl, chromanyl, benzothienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indazolyl, benzimidazolyl, quinazolinyl, quinoxalinyl, 1,3-benzodioxolyl, benzodioxanyl, tetrazolyl, benzothiazolyl and/or indazolyl group.

18. A use as claimed in Claim 17, wherein R^1 and/or R^2 represent an optionally substituted pyrrolidinyl, piperidinyl, oxindolyl, phenyl, naphthyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, indolyl, indolinyl, isoindolinyl, quinolinyl, 1,2,3,4-

tetrahydroquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinolizinyl, benzofuranyl, isobenzofuranyl, chromanyl, benzothienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indazolyl, benzimidazolyl, quinazolinyl, quinoxalinyl, 1,3-benzodioxolyl and/or benzodioxanyl group.

19. A use as claimed in Claim 17 or Claim 18, wherein the optional substituents are selected from halo, $-NO_2$, cyano, C_{1-6} alkyl (which alkyl group may be linear, branched, cyclic, part-cyclic, unsaturated and/or optionally substituted with one or more fluoro group), phenyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, $-OR^{18}$, $-N(R^{18})R^{19}$, $-C(O)R^{18}$, $-C(O)OR^{18}$ $-C(O)N(R^{18})R^{19}$, $-S(O)_mR^{20}$, $-S(O)_2N(R^{18})R^{19}$ and/or $-N(R^{18})S(O)_2R^{20}$, wherein R^{18} and R^{19} independently represent H, phenyl or C_{1-6} alkyl, R^{20} represents C_{1-4} alkyl and m represents 0, 1 or 2.

20. A use as claimed in Claim 19, wherein the substituents are selected from fluoro, chloro, bromo, cyano, hydroxyl, amino, $-NO_2$, C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, phenoxy, trifluoromethyl, $-N(H)SO_2CH_3$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, $-SO_2N(H)CH_3$, $-N(CH_3)_2$ and morphoinyl.

21. A use as claimed in Claim 20, wherein the substituents are selected from fluoro, chloro, bromo, cyano, hydroxyl, amino, $-NO_2$, C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, phenoxy, trifluoromethyl, $-N(H)SO_2CH_3$, $-SO_2NH_2$ and $-SO_2N(CH_3)_2$.

22. A use as claimed in any one of the preceding claims, wherein R^1 represents thienyl; pyrazolyl, which pyrazolyl group is substituted by one or more methyl groups or is unsubstituted; pyridyl, which pyridyl group is substituted by one or more substituents selected from bromo, chloro, methyl and hydroxyl or is unsubstituted; or phenyl, which phenyl group is

optionally substituted by one or more substituents selected from methyl, *t*-butyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, phenyl, hydroxyl, amino, $-NO_2$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, $-SO_2N(H)CH_3$ and $-N(CH_3)_2$.

23. A use as claimed in Claim 22, wherein R^1 represents thienyl; unsubstituted pyrazolyl; unsubstituted pyridyl; or phenyl optionally substituted by one or more substituents selected from methyl, *t*-butyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, phenyl, hydroxyl, amino, $-NO_2$, $-SO_2NH_2$ and $-SO_2N(CH_3)_2$.

24. A use as claimed in any one of the preceding claims, wherein R^2 represents 2-pyridyl, 4-pyridyl, 2-quinoxalinyl, or phenyl, which phenyl group is optionally substituted by one or more substituents selected from methyl, phenoxy, $-N(H)SO_2CH_3$, methoxy, fluoro, chloro, bromo, trifluoromethyl, hydroxyl, $-NO_2$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, cyano, morpholinyl, $-N(CH_3)_2$ and ethyl.

25. A use as claimed in Claim 24, wherein R^2 represents 2-pyridyl or phenyl, which phenyl group is optionally substituted by one or more substituents selected from methyl, phenoxy, $-N(H)SO_2CH_3$, methoxy, fluoro, chloro, bromo, trifluoromethyl, hydroxyl, $-NO_2$, $-SO_2NH_2$ and $-SO_2N(CH_3)_2$.

26. A compound of formula I as defined in any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical, provided that, when R^4 represents H and:

(A) R^3 represents H and:

(I) R^2 represents phenyl, then R^1 does not represent 2-furanyl, 4-pyridyl, 3-(5-methylisooxazolyl), phenyl, or 3-nitro-, 2-

hydroxy-, 2-hydroxy-3-methyl-, 4-(thienyl)-, 2-hydroxy-5-methyl- or 4-hydroxyphenyl;

(II) R^2 represents 4-chlorophenyl, then R^1 does not represent 2-furanyl, 4-pyridyl, phenyl, or 2-hydroxy-5-methyl-, 4-hydroxy-, 2-hydroxy-3-methyl- or 2-hydroxyphenyl;

(III) R^2 represents 4-methylphenyl, then R^1 does not represent 4-pyridyl, phenyl, or 3-nitro-, 2-hydroxy-5-methyl-, 4-hydroxy-, 2-hydroxy- or 4-(thienyl)phenyl; or

(IV) R^2 represents 2-furanyl or 2-benzofuranyl, then R^1 does not represent 4-pyridyl or 3-(5-methylisooxazolyl); and

(B) R^3 represents methyl and:

(1) R^2 represents phenyl, then R^1 does not represent *N*-(4-bromophenyl)-2-amino-, *N*-(2-methoxyphenyl)-2-amino-, *N*-(2-ethoxyphenyl)-2-amino-, *N*-(3-chlorophenyl)-2-amino-, *N*-(4-methylphenyl)-2-amino-, *N*-(3-methylphenyl)-2-amino-, *N*-(2-methylphenyl)-2-amino- or *N*-(phenyl)-2-aminophenyl; or

(2) R^2 represents 4-chlorophenyl, then R^1 does not represent 4-pyridyl, phenyl, or 3-nitro-, 2-hydroxy-5-methyl-, 4-hydroxy-, 2-hydroxy- or 2-hydroxy-3-methylphenyl.

27. A pharmaceutical formulation including a compound as defined in Claim 26, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

28. A compound as defined in Claim 26, or a pharmaceutically-acceptable salt thereof, with the additional provisos that, when R^4 represents H, R^2 represents phenyl and:

(a) R^3 represents H, then R^1 does not represent 2-pyridyl, or 3-bromo-, 3,4-dimethoxy- or 2-hydroxy-5-bromophenyl; and

(b) R^3 represents methyl, then R^1 does not represent 4-methoxyphenyl.

29. A use as claimed in any one of Claims 1 to 25 wherein the lipoxygenase is 15-lipoxygenase.

30. A use as claimed in any one of Claims 1 to 25 or 29, wherein the disease is inflammation and/or has an inflammatory component.

31. A use as claimed in Claim 30 wherein the inflammatory disease is asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, allergic disorders, rhinitis, inflammatory bowel disease, ulcers, inflammatory pain, fever, atherosclerosis, coronary artery disease, vasculitis, pancreatitis, arthritis, osteoarthritis, rheumatoid arthritis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes, autoimmune diseases, Alzheimer's disease, multiple sclerosis, sarcoidosis, Hodgkin's disease or another malignancy.

32. A method of treatment of a disease in which inhibition of the activity of a lipoxygenase is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound of formula I as defined in any one of Claims 1 to 28, or a pharmaceutically-acceptable salt thereof, to a patient suffering from, or susceptible to, such a condition.

33. A combination product comprising:

(A) a compound of formula I, as defined in any one of Claims 1 to 28, or a pharmaceutically-acceptable salt thereof; and

(B) another therapeutic agent that is useful in the treatment of inflammation,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

34. A pharmaceutical formulation including a compound of formula I as defined in any one of Claims 1 to 28, or a pharmaceutically-acceptable salt thereof, another therapeutic agent that is useful in the treatment of inflammation, and a pharmaceutically-acceptable adjuvant, diluent or carrier.

35. A kit of parts comprising components:

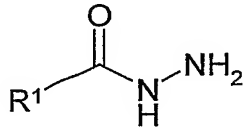
(a) a pharmaceutical formulation including a compound of formula I as defined in any one of Claims 1 to 28, or a pharmaceutically-acceptable salt thereof in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent that is useful in the treatment of inflammation in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

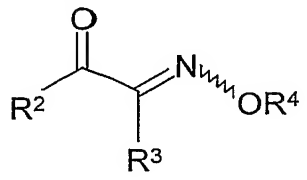
36. A process for the preparation of a compound as defined in Claim 28, which comprises:

(i) reaction of a compound of formula II,



II

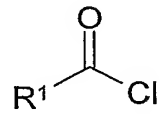
wherein R^1 is as defined in Claim 1, or an acid addition salt thereof, with a compound of formula III,



III

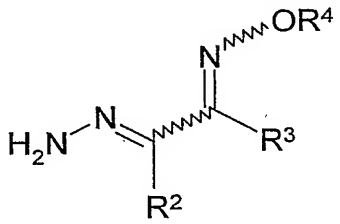
wherein the squiggly bond, R^2, R^3 and R^4 are as defined in Claim 1;

(ii) reaction of a compound of formula IV,



IV

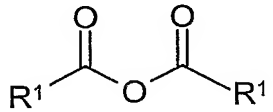
wherein R^1 is as defined in Claim 1 with a compound of formula V,



V

wherein the squiggly bonds, R^2, R^3 and R^4 are as defined in Claim 1;

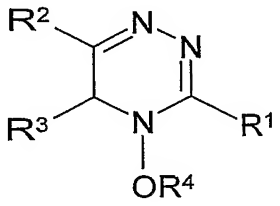
(iii) reaction of a compound of formula VI,



VI

wherein R^1 is as defined in Claim 1 with a compound of formula V as defined above;

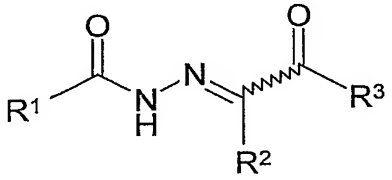
(iv) ring opening of a compound of formula VII,



VII

wherein R^1, R^2, R^3 and R^4 are as defined in Claim 1;

(v) reaction of a compound of formula VIII,



VIII

wherein the squiggly bond, R^1, R^2 and R^3 are as defined in Claim 1 with a compound of formula IX,

$$R^4ONH_2 \qquad \text{IX}$$

wherein R^4 is as defined in Claim 1, or an acid addition salt thereof;

(vi) for compounds of formula I in which R^4 represents optionally substituted C_{1-6} alkyl, reaction of a corresponding compound of formula I in which R^4 represents H with a compound of formula X,

$$R^{4a}L^1 \qquad X$$

wherein L^1 is a suitable leaving group and R^{4a} is C_{1-6} alkyl optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl, cyano, $-NO_2$, $-ONO_2$, $-N(R^{14})R^{15}$, $-OR^{15}$, =O, aryl or heteroaryl; or

(vii) reaction of a compound of formula XI,

$$R^1L^2 \qquad XI$$

wherein L^2 is a suitable leaving group and R^1 is as defined in Claim 1 with a compound of formula V as defined above in the presence of carbon monoxide or another suitable CO source.